REMARKS

Applicants acknowledge with appreciation the Office's withdrawal of the rejection of claims 1, 5, 7, and 11 under 35 U.S.C. § 102(b) as being anticipated by Duffy. Applicants also acknowledge with appreciation the Office's withdrawal of the rejection of claims 1, 5-7, 9-11, and 13 under 35 U.S.C. § 102(b) as being anticipated by Zhu et al. Applicants also acknowledge with appreciation the Office's withdrawal of the rejection of claims 1, 5, 7, 8, 11, and 12 under 35 U.S.C. § 102(b) as being anticipated by Hertz et al.

Upon entry of the present amendment, claims 4-9, 14, and 17-23 are pending in the present application. Claims 5-9 and 17-23 are under consideration. Claims 4 and 14 have been withdrawn from consideration. In the present amendment, Applicants cancel claims 1, 10-13, 15, and 16 without prejudice or disclaimer, and add new claims 19-23 as follows:

Claim 19 depends from claim 8 and recites an embryonic stem cell. Support for this amendment is found in the specification, for example, at page 3, lines 15-16, and figure 5 (showing DNA methylation patterns obtained by RLGS for embryonic stem cells).

Claims 20 and 21 each depend from claim 5, and recite that the differentiation state of the cell, tissue, or nucleus of known differentiation state is differentiated, or undifferentiated, respectively. Support for this amendment is found in the specification, for example, at page 3, lines 15-17, and figure 5 (showing DNA methylation patterns obtained by RLGS for differentiated and undifferentiated embryonic stem cells and for differentiated and undifferentiated trophoblast stem cells).

Claim 22 recites a method of identifying a test cell, tissue, or nucleus by comparing the DNA methylation pattern of a test cell, tissue, or nucleus with that of a certain known cell, tissue,

or nucleus, wherein a match identifies the test cell, tissue, or nucleus as the certain known cell, tissue, or nucleus. Claim 22 further recites that the known cell, tissue, or nucleus is selected from undifferentiated embryonic stem cell, differentiated embryonic stem cell, undifferentiated trophoblast stem cell, differentiated trophoblast stem cell, kidney, placenta, brain, and sperm. Support for this amendment is found in the specification, for example, at page 15, line 27 to page 17, line 12, and figure 7 (an example and flow chart showing cell identification processing, wherein information on methylation patterns was analyzed by the RLGS technique, and wherein the known cell, tissue, or nucleus was undifferentiated embryonic stem cell, differentiated embryonic stem cell, undifferentiated trophoblast stem cell, differentiated trophoblast stem cell, kidney, placenta, brain, and sperm).

Thus, the foregoing new claims do not add new matter.

I. Rejection of Claims 1, 10-13, 15, and 16 Under 35 U.S.C. § 112, paragraph 2

The Office rejected claims 1, 10-13, 15, and 16 under 35 U.S.C. § 112, paragraph 2 as allegedly indefinite because, according to the Office, it was not clear whether "the cell-, tissue-, or nucleus-specific DNA methylation pattern" referred to the pattern of the test cell or the known cell. Without acquiescing to the Office's rejection and arguments, Applicants have canceled claims 1, 10-13, 15, and 16. Thus, the rejection of these claims is moot.

II. Rejection of Claims 1 and 10 under 35 U.S.C. § 102(e)

The Office rejected claims 1 and 10 under 35 U.S.C. § 102(e) as allegedly being anticipated by Olek et al., U.S. Patent No. 6,214,556. Without acquiescing to the Office's rejection and arguments, Applicants have canceled claims 1 and 10. Thus, this rejection is moot.

III. Rejection of Claims 1, 5-7, 9, 11, 13, and 15-18 Under 35 U.S.C. § 103(a)

The Office rejected claims 1, 5-7, 9, 11, 13, and 15-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olek et al. in view of Ohgane et al., Dev. Gen. 22:132-140 (1998). According to the Office, "Olek et al. shows in the abstract and throughout a method of comparing methylation fingerprint patterns of different cells to classify a test cell . . . [and that] thousands or millions of methylcytosine locations are assayed to form the fingerprints." Action at page 5. And, according to the Office, "Ohgane et al. shows in the abstract and throughout, . . . comparison of methylation patterns . . . [and] conclude that cells of different differentiation states in the placenta have different methylation patterns." *Id.* at page 6. The Office then states that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the identification method of Olek et al. to identify differentiation states of cells because Ohgane et al. shows that differentiation states correlate with different methylation patterns." *Id.* The Office further states that it would have been "obvious to use the RLGS method to determine methylation patterns because Ohgane et al. shows that the RLGS method allows for determination of thousands of sites of methylation." *Id.*

Applicants respectfully traverse the rejection. First, the rejection is moot as to claims 1, 11, 13, 15, and 16, which have been canceled without prejudice or disclaimer. Second, and more importantly, the Office has not set forth a *prima facie* case of obviousness. According to the M.P.E.P. § 2143.03 at 2100-133, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. . . . All words in a claim must be considered in judging the patentability of that claim against the prior art." (citations omitted). Applicants contend that there is no *prima facie* case of obviousness because, *inter alia*, the combined disclosures of Olek et al. and Ohgane et al. do not teach or suggest all of the limitations of independent claim 5. Specifically, the combined disclosures do not teach or

suggest "identifying the differentiation state of a test cell, tissue, or nucleus," nor do the combined disclosures teach or suggest "a differentiation state-specific DNA methylation pattern," nor do the combined disclosures teach or suggest "comparing the DNA methylation pattern for the test cell, tissue, or nucleus with a differentiation state-specific DNA methylation pattern for a cell, tissue, or nucleus of known differentiation state."

First, the combined disclosures do not teach or suggest "identifying the differentiation state of a test cell, tissue, or nucleus." Olek is completely silent with respect to differentiation states. And, while Ohgane et al. concludes that "modification of CpG islands by cytosine methylation is involved in differentiation of the trophoblast cell lineage," the reference is silent with respect to identifying the differentiation state of a test cell, tissue, or nucleus. Showing that methylation is "involved in differentiation" is not the same as identifying the differentiation state. Because the combined disclosures are silent on "identifying the differentiation state of a test cell, tissue, or nucleus," they do not teach or suggest this limitation of independent claim 5.

Moreover, neither Olek et al., nor Ohgane et al., nor the combined disclosures teach or suggest a "differentiation state-specific DNA methylation pattern." As discussed above, Olek et al. is silent about differentiation states, and thus does not teach or suggest a "differentiation state-specific DNA methylation pattern." And, Ohgane et al. show that "methylation is involved in differentiation," and that "RLGS will be adaptable for systematic detection of imprinted genes, which are involved in normal placental growth and differentiation." *See* Ohgane et al. p. 139.

The involvement of methylation with differentiation is not the same as a "differentiation state-specific DNA methylation pattern." Ohgane et al. indicate that when methylation is involved in differentiation, "there are several CpG islands that differ in methylation between the junctional and labyrinth zones," and "methylation states . . . change dramatically during

embryonic development in a stage- and spatio-specific manner." Ohgane et. al. at 139. But a recognition of such changes does not constitute a "differentiation state-specific DNA methylation pattern."

The difference between the two can be appreciated by examining the data in Figure 5 of the specification. For example, Figure 5 shows several spots that clearly appear in undifferentiated embryonic stem cells but disappear in differentiated embryonic stem cells. Exemplary spots include spots 9 and 10. Thus, it can be said that spots 9 and 10 represent genes whose methylation states change dramatically during embryonic development. However, further examination of figure 5 reveals that spots 9 and 10 cannot constitute a "differentiation state-specific DNA methylation pattern" because spots 9 and 10 clearly appear in kidney, but disappear in sperm and brain. Kidney, sperm, and brain are each known in the art as differentiated tissues. Thus, the data for spots 9 and 10 in figure 5 demonstrates that methylation that is "involved in differentiation" is not the same as a "differentiation state-specific DNA methylation pattern." Ohgane et al., therefore, at most merely shows that methylation is involved in differentiation, but does not teach or suggest a "differentiation state-specific DNA methylation pattern." Accordingly, the combined disclosures of Olek et al. and Ohgane et al. do not teach or suggest this limitation of independent claim 5.

Finally, neither Olek et al. nor Ohgane et al. teach or suggest "comparing the DNA methylation pattern for the test cell, tissue, or nucleus with a differentiation state-specific DNA methylation pattern for a cell, tissue, or nucleus of known differentiation state." As the Office stated, "Olek et al. does not explicitly show comparison of cells of different differentiation states, . . . or determining methylation sites by use of the RLGS method." Action at pages 5-6. Moreover, Ohgane et al. is silent about comparing a DNA methylation pattern for a test cell, tissue, or nucleus with a differentiation state-specific DNA methylation pattern. Accordingly,

the combined disclosures fail to teach or suggest this limitation of independent claim 5. Since the combined disclosures of Olek et al. and Ohgane et al. do not teach or suggest all of the claim limitations of independent claim 5, claim 5 is not obvious in view of these combined disclosures, nor are claims 6, 7, 9, 17, and 18, which ultimately depend from claim 5. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5-7, 9, 17, and 18 under 35 U.S.C. § 103(a).

IV. Rejection of Claims 1, 5, 8, and 12 Under 35 U.S.C. § 103(a)

The Office rejected claims 1, 5, 8, and 12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Olek et al. in view of Ohgane et al. as applied to claims 1, 5-7, 9, 11, 13, and 15-18, and further in view of Onno et al., Tissue Antigens 49:356-364 (1997). Action at page 6. The Office notes that Olek et al. and Ohgane et al. do not show identification of stem cells, but, according to the Office, "Onno et al. shows . . . that CD34+ hematopoietic stem cells have a different methylation pattern than CD2+ lymphocytes." Action at page 7. The Office concludes that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the identification method of Olek et al. in view of Ohgane et al. . . . to identify stem cells because Onno et al. shows that stem cells have characteristic methylation patterns that allow for their identification by determination of methylation fingerprints." *Id.*

Applicants respectfully traverse this rejection. First, claims 1 and 12 have been canceled without prejudice or disclaimer rendering the rejection moot with respect to these claims. Second, the Office has again not set forth a *prima facie* case of obviousness. The combined disclosures do not teach or suggest all of the claim limitations, and therefore, Applicants contend that the Office has not shown a *prima facie* case of obviousness. As discussed at length above, the combined disclosures of Olek et al. and Ohgane et al. do not teach or suggest "identifying the differentiation state of a test cell, tissue, or nucleus," nor a "differentiation state-specific DNA

methylation pattern," nor "comparing the DNA methylation pattern for the test cell, tissue, or nucleus with a differentiation state-specific DNA methylation pattern for a cell, tissue, or nucleus of known differentiation state." Moreover, Onno et al. fail to teach or suggest any of these limitations with respect to stem cells.

Onno et al. do not teach or suggest identifying the differentiation state of a stem cell, tissue, or nucleus. Onno et al. merely examine methylation of ONE gene, HLA-G, and compare the methylation pattern of that one gene in CD34+ hematopoietic stem cells (where it is not expressed) to the methylation pattern in CD2+ lymphocytes (where it is expressed). *See, e.g.*, Onno et al. abstract. The authors stated some of their results in the abstract, noting that "[t]he general patterns of CpG methylation in the 5' part of the gene were found to be **similar** for CD34+ cells and CD2+ lymphocytes: the distribution of methylation was not uniform across the 63 CpG sites." (Emphasis added). The similarity of the methylation patterns in the HLA-G gene in CD34+ hematopoietic stem cells and CD2+ lymphocytes does not teach or suggest that the methylation state of this gene could be used to identify the differentiation state of the stem cell; in fact, it suggests the opposite.

Nowhere does Onno et al. teach or suggest a methylation pattern that is differentiation state-specific such that it could be used to identify the differentiation state of a test cell. Indeed, the clonal data for methylation patterns in CD34+ hematopoietic stem cells and CD2+ lymphocytes presented in tables 2 and 3 (Onno et al. at page 361-362) teaches away from the concept of a differentiation state-specific DNA methylation pattern. The data in these two tables shows a high degree of clonal variability and, as explained by the authors, "the methylation pattern of individual clones was heterogeneous within each hematopoietic population." *Id.* at page 362. Although "on average, the clones derived from CD2+ lymphocytes were more methylated that the CD34+ cells clones," *id.* at 362, the methylation patterns would hardly

constitute a "differentiation state-specific DNA methylation pattern" due to the heterogeneity in methylation patterns observed between clones of the same lineage.

Finally, while Onno et al. do compare the methylation patterns of CD34+ and CD2+ cells for ONE gene, nowhere do Onno et al. teach or suggest the identification of the differentiation state of a test cell by comparing its methylation pattern to that of a cell of known differentiation state. Indeed, as discussed above, Onno et al. teaches away from this possibility by disclosing the "similarity" between the CD34+ and CD2+ methylation patterns for HLA-G. Accordingly, the combined disclosures of Olek et al. in view of Ohgane et al. as applied to claims 1, 5-7, 9, 11, 13, and 15-18, and further in view of Onno et al. do not teach or suggest all of the claim limitations of independent claim 5, nor of claim 8, which depends from claim 5 and is directed to stem cells. Thus, claims 5 and 8 are not obvious in view of these combined disclosures, and Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5 and 8 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6749 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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Dated: July 15, 2005

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